D9 respiratory tracts and related organs, diseases of other internal and external tissue surfaces, tissue surfaces exposed during surgery, and microbial or parasitic infection.

REMARKS

Applicants will address each of the Examiner's objections and rejections in the order in which they appear in the Office Action

I. Response to Amendment

In the Office Action, the Examiner objects to the amendment filed "7-22-02" (i.e. Revised Amendment B having a certificate of mailing of July 16, 2002) because it allegedly introduced new matter into the disclosure. In particular, the Examiner states that fluorescein should not have been removed from Table 1 and requests cancellation of the new matter. While Applicants do not agree, in order to advance the prosecution of this application. Applicants will comply with the Examiner's request.

While, the undersigned is unsure of the procedure for doing this, it is requested that Table 1 as originally filed be submitted back into the specification, as shown herein. This should overcome the Examiner's objection, and it is requested that it now be withdrawn.

II. Claim Rejections - 35 U.S.C. §112

The Examiner also rejects Claim 12 under 35 U.S.C. §112, second paragraph, as being indefinite, for a minor informality in the preamble of the claim. Applicants have amended the preamble of Claim 12 herein and believe that this objection has now been overcome. Accordingly, it is requested that the objection now be withdrawn.

III. Claim Rejections - 35 U.S.C. §102

A. Rejection Over Gaboury et al.

The Examiner continues to reject Claims 1, 5-6, 13-14, 16-17, 19, 21-22, 25-26 and 30-35 under 35 U.S.C. §102(b) as being anticipated by two Gaboury et al. references (i.e., US 5,556,992 and US 5,773,460, henceforth Gaboury). This rejection is respectfully traversed.

In the Office Action, the Examiner states that Applicants have argued, in their response filed "7-22-02" [i.e. Revised Amendment B], that the claimed halogenated xanthenes of the present application are of a distinctly different family of compounds from those claimed in the present invention. The Examiner then cites isolated passages from the specification of the present application in support of this continued rejection.

Applicants disagree with the Examiner's interpretation of the specification for a number of reasons, as set forth in Revised Amendment B and including the following reasons:

- Table 1 and Figs. 1a and 1b of the present application show that the "halogenated xanthenes", as defined in the present application, are weakly acidic (i.e., anionic) derivatives of fluorescein, having a carboxyl group at position 2', and hydroxy groups at positions 6 and 3. In contrast, the rhodamine derivatives of Gaboury constitute weakly basic (i.e., cationic) derivatives of rhodamine.

- The rhodamines of Gaboury contain three (3) oxygen atoms: two oxygen atoms in a carboxyl group at position 2', and one heterocyclic oxygen between positions 4 and 5. As is clearly illustrated in Figs. 1a and 1b of the present application, *all* halogenated xanthenes contain at least five (5) oxygen atoms, divided between the carboxyl group at position 2', the oxygen functionalities at positions 6 and 3, and a heterocyclic oxygen located between positions 4 and 5.

It is well established law that claims are interpreted in light of the specification and drawings. The present application clearly defines the chemical structure of the "halogenated xanthenes" (i.e., as illustrated in Figs. 1a and 1b), and this chemical structure is clearly distinguishable from that of the "rhodamine derivatives" of Gaboury. Such distinction would be clear to one of ordinary skill in the art. Hence, the claimed invention is clearly distinguishable form Gaboury.

However, in order to advance the prosecution of this application , Applicants have amended independent Claims 1, 13, 17, 21, 32, 36 and 37 to recite the specific chemical species claimed. The structure of each of these species is distinctly different from any of those disclosed by Gaboury. Accordingly, for at least these reasons, the Examiner's basis for rejection has been overcome.

Therefore, it is respectfully submitted that Gaboury does not disclose or suggest the claims of the present application, and the claims are patentable thereover. Accordingly, it is requested that this rejection be withdrawn.

B. Rejection Over Kopia

The Examiner also continues to reject Claims 1, 5-12, 21, and 25-31 under 35 U.S.C. §102(e) as being anticipated by Kopia et al. This rejection is also respectfully traversed.

In the Office Action, the Examiner contends that "a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." Applicants respectfully submit that the claims of the present application are patentably distinct from Kopia.

In particular, Kopia describe certain uses for immunoconjugates of fluorescein. Independent Claims 1 and 21 have been amended, as described supra, and thereby eliminate any possible

ambiguity regarding the claimed invention relative to such fluorescein derivatives. More particularly, the precise definition of the claimed halogenated xanthenes in the claims and their derivatives are clearly different than the fluorescein derivatives of Kopia. Specifically, since Kopia's fluorescein derivatives do not contain halogen atoms, they cannot be confused with the claimed halogenated xanthenes, all of which contain multiple halogen atoms.

Hence, these amendments to independent Claims 1 and 21 clearly overcome the Examiner's basis for rejection of these claims, and all those claims dependent thereupon.

Therefore, Kopia fails to disclose or suggest the claimed invention, and thus it is respectfully requested that this rejection be withdrawn.

Accordingly, for the above-stated reasons, the claims of the present application are not anticipated by the cited references, and it is requested that the §102 rejections be withdrawn.

IV. Claim Rejections - 35 U.S.C. §103(a)

The Examiner also continues to reject Claims 2, 7-10, 15, 18, 23, 27-29, and 36-38 under 35 U.S.C. §103(a) as being unpatentable over Gaboury. This rejection is also respectfully traversed.

As described supra in reference to rejection of claims under 35 U.S.C. 102(b), Applicants have amended independent Claims 1, 13, 17, 21, 32, 36 and 37 to recite specific chemical species claimed. Further, as described supra, such species are clearly distinct from those disclosed by Gaboury. Hence, these amendments to independent Claims 1, 13, 17, 21, 32, 36 and 37 overcome the Examiner's basis for rejection of each of the rejected dependent claims.

Accordingly, it is respectfully requested that the rejection of these claims under 35 U.S.C. §103 as being unpatentable over Gaboury be withdrawn.

V. New Rejection - 35 U.S.C. §102

The Examiner also has issued a new rejection rejecting Claims 1, 3-6, 13, 21, 23-26, 32 and 36-38 under 35 U.S.C. §102(b) as being anticipated by Goers et al. This rejection is also respectfully traversed.

Dependent Claims 5-6 and 25-26, as filed, described alternate embodiments of the present invention that further comprise conjugation of a halogenated xanthene to a chemical or biological targeting moiety. Their respective independent claims (i.e., Claims 1 and 21), require no such conjugation, and thus cannot be anticipated, by Goers. In fact, such conjugation was prescribed, for example, only as a way to further improve the already favorable pharmacokinetic properties of the halogenated xanthenes, as described by the following passages from the present application:

> "As an example of these desirable chemical, biochemical, and physical properties, the inventors have found that the prototypical halogenated xanthene, Rose Bengal, will accumulate preferentially in (i.e. target) some tumors and other diseased tissues and pathogens, has negligible dark cytotoxicity, high light cytotoxicity upon illumination with visible light, relatively low cost, and the ability to clear rapidly from the body." (p. 7, lines 18-22)

> "...the facility with which the halogenated xanthenes target specific tissues or other sites *can be further optimized* by attachment of specific functional derivatives at positions R^1 and R^2, so as to change the chemical partitioning or biological activity of the agent. For example, attachment of one targeting moiety or more at positions R^1 or R^2 can be used to improve targeting to specific tissues, such as cancerous tumor tissues or sites of localized infection. An example of this is esterification at position R^1 with a short aliphatic alcohol, such as n-hexanol, to produce a derivatized agent exhibiting enhanced partitioning into lipid-rich tumor tissues." (p. 8, lines 1-7, emphasis added)

These passages teach that the halogenated xanthenes are useful, as claimed in independent Claims 1 and 21, in their native (i.e., non-conjugated) form. It is only as an additional refinement

that conjugation is taught. In contrast, Goers does not teach any such non-conjugated use of any halogenated xanthene.

Thus, in contrast to the teachings of Goers, which *require conjugation to an antibody or antibody fragment*, the present invention (1) not only teaches that such *conjugation is unnecessary* (i.e., the halogenated xanthenes may be used successfully without conjugation), but (2) it further teaches that, if such conjugation methods are utilized, the general approach of the present invention is *far broader* than that taught by Goers (i.e., conjugation of the halogenated xanthenes to other targeting moieties, such as esterification with a short aliphatic alcohol, as described supra, is a useful form of conjugation for enhancing disease-specific targeting). The extremely narrow teachings of Goers (i.e., comprising an antibody conjugated to Rose Bengal) therefore cannot anticipate the broad teachings and claims of the present invention (which include use of non-conjugated halogenated xanthenes along with conjugation to a broad range of chemical or biological moieties).

Further, Goers' generic description of "photoradiation therapy" (i.e., col. 28, lines 45-68) does not disclose the therapeutic uses of the halogenated xanthenes as taught by the present application. Rather, the above-cited passage, taken together with the other passages cited by the Examiner, only provides vague descriptions of possible uses of Goers' special antibody-conjugate agents (including antibody-conjugates comprising Rose Bengal coupled to an antibody or antibody fragment).

Most importantly, by failing to teach a topically-applicable medicament, Goers teaches away from the fundamental subject matter of each of the pending independent claims. Specifically, Goers states:

> "In vivo administration may involve use of therapeutic agents of antibody therapeutic agent conjugates in any suitable adjuvant including serum or physiological saline, with or without another

> protein, such as human serum albumin.... Route of administration may be parenteral, with intravenous administration generally preferred." (col. 28, lines 33-42)

Parenteral administration (i.e., injection into the body), as taught by Goers, would not be readily confused with topical administration, as claimed in the present application. Moreover, knowledge of any such agents for parenteral administration would not lead one of ordinary skill in the art to develop other, unrelated topically-applicable medicaments, as claimed in the present application.

In order to advance the prosecution of this application, Applicants have amended Claims 5 and 25, and have canceled Claims 6 and 26. Such amendment removes any alleged potential superficial similarity between the teachings of Goers and the claimed invention. Such amendments, when considered in conjunction with the aforementioned arguments, demonstrate that independent Claims 1, 13, 21, 32, 36 and 37, and all those dependent thereupon, are patentable over Goers. Accordingly, it is respectfully requested that this rejection be withdrawn.

VI. New Rejection - 35 U.S.C. §103

The Examiner also has a new further rejection rejecting Claims 16-19, 30 and 34 under 35 U.S.C. 103 as obvious over Goers et al. in view of Neckers. This rejection is also respectfully traversed.

As stated supra, Goers fails to teach a topically-applicable medicament, which is a fundamental subject matter of each of the rejected claims. Similarly, Neckers also fails to teach such a medicament. Thus, irrespective of any teachings of Neckers concerning certain physical properties of certain members of the halogenated xanthenes, any alleged combination of these references would fail to draw one of ordinary skill to the present invention. Knowing that Rose

Bengal absorbs light at 549 nm, as taught by Neckers, does not cure failure of the teachings of Goers, which states:

> "In vivo administration may involve use of therapeutic agents of antibody therapeutic agent conjugates in any suitable adjuvant including serum or physiological saline, with or without another protein, such as human serum albumin.... Route of administration may be parenteral, with intravenous administration generally preferred." (col. 28, lines 33-42)

Parenteral administration (i.e., injection into the body), as taught by Goers, would not be readily confused with topical administration, as recited in the claimed invention. Adding light at 549 nm to the mix would not cure this shortcoming nor draw one to the present invention.

Accordingly, for at least these reasons, the Examiner's rejection of Claims 16-19, 30 and 34 under 35 U.S.C. 103(a) as being obvious over Goers in view of Neckers is inappropriate, and it is respectfully requested that it be withdrawn.

VII. Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this response, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: April 17, 2003

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Marked-up copy of the amendments made herein:

IN THE CLAIMS:

Please amend the claims as follows:

Claim 1 (twice amended). A topically-applicable photodynamic medicament, the medicament comprising at least one halogenated xanthene as a photoactive component, wherein said halogenated xanthene includes at least one compound selected from the group consisting of Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein, and wherein said medicament is useful for treatment of diseases of human and animal tissue.

Cancel Claim 4.

Claim 5 (amended). The medicament of Claim 1 further comprising at least one chemical or biological targeting moiety coupled to said halogenated xanthene, wherein said targeting moiety is selected from the group consisting of deoxyribonucleic acids (DNA), ribonucleic acids (RNA), amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors, carbohydrate complexing agents, lipid receptors, lipid complexing agents, protein receptors, protein complexing agents, chelators, encapsulating vehicles, short-chain aliphatic hydrocarbons, long-chain aliphatic hyrdocarbons, aromatic hydrocarbons, aldehydes, ketones, alcohols, esters, amides, amines, nitriles, azides, hydrophilic moieties and hydrophobic moieties.

Cancel Claim 6.

Claim 12 (twice amended). The medicament [method] of Claim 1 wherein said medicament is activated using light having a wavelength of between approximately 500 nm and 600 nm.

Claim 13 (twice amended). Use of a halogenated xanthene as a photoactive component in the preparation of a topical medicament for treatment of human and animal tissue using photodynamic therapy, wherein said halogenated xanthene includes at least one compound selected from the group consisting of Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein.

Claim 17 (amended). Use of a halogenated xanthene comprising:

topically administering a therapeutically effective amount of a halogenated xanthene to or proximate to human or animal tissue and photoactivating the halogenated xanthene present within or proximate to said tissue, wherein said halogenated xanthene includes at least one compound selected from the group consisting of Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein.

Claim 21 (amended). A pharmaceutical composition for topical administration comprising a halogenated xanthene for treatment using photodynamic therapy, wherein said halogenated xanthene includes at least one compound selected from the group consisting of Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or

Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein.

Cancel Claim 24.

Claim 25 (amended). The pharmaceutical composition of Claim 21 further comprising at least one chemical or biological targeting moiety coupled to said halogenated xanthene, wherein said targeting moiety is selected from the group consisting of deoxyribonucleic acids (DNA), ribonucleic acids (RNA), amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors, carbohydrate complexing agents, lipid receptors, lipid complexing agents, protein receptors, protein complexing agents, chelators, encapsulating vehicles, short-chain aliphatic hydrocarbons, long-chain aliphatic, aromatic hydrocarbons, aldehydes, ketones, alcohols, esters, amides, amines, nitriles, azides, hydrophilic moieties and hydrophobic moieties.

Cancel Claim 26.

Claim 32 (twice amended). A method of treating diseased tissue comprising:

topically applying a medicament including at least one halogenated xanthene to or proximate to diseased human or animal tissue, wherein said halogenated xanthene includes at least one compound selected from the group consisting of Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein; and

illuminating said human or animal tissue with light to photoactivate said halogenated xanthene present within or proximate to said tissue.

Claim 36 (twice amended). A topically-applicable medicament comprising at least one halogenated xanthene as a photoactive component, wherein said halogenated xanthene includes at least one compound selected from the group consisting of Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein, and, wherein such medicament is useful for photodynamic treatment of human and animal tissue.

Claim 37 (twice amended). A topically-applicable medicament comprising at least one halogenated xanthene as a primary active component, wherein said halogenated xanthene includes at least one compound selected from the group consisting of Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein, and wherein such medicament is useful for photodynamic treatment of indications selected from the group consisting of diseases of the skin and related organs, diseases of the mouth and digestive tract and related organs, diseases of the urinary and reproductive tracts and related organs, diseases of the respiratory tracts and related organs, diseases of other internal and external tissue surfaces, tissue surfaces exposed during surgery, and microbial or parasitic infection.